
Inactivation of the RB family prevents thymus involution and promotes thymic function by direct control of Foxn1 expression.

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Public Summary:

The thymus is the site of T cell maturation and is where functional T cells are selected. The thymus grows rapidly early in life and then begins to shrink in a process known as involution. Thymic involution during aging is a major cause of decreased production of T cells and reduced immunity. Here we show that inactivation of the three genes that make up the Rb family genes in young mice prevents thymic involution and results in an enlarged thymus that continues to produce functional T cells. This phenotype originates from the expansion of functional thymic epithelial cells (TECs) and does not result in cancer. Thus, the RB family controls T cell production via regulation of TEC number. Our studies identify a new mechanism regulating thymus size and immune function and provides potential therapeutic targets to regenerate involuted thymus and improve immune function.

Scientific Abstract:

Thymic involution during aging is a major cause of decreased production of T cells and reduced immunity. Here we show that inactivation of Rb family genes in young mice prevents thymic involution and results in an enlarged thymus competent for increased production of naive T cells. This phenotype originates from the expansion of functional thymic epithelial cells (TECs). In RB family mutant TECs, increased activity of E2F transcription factors drives increased expression of Foxn1, a central regulator of the thymic epithelium. Increased Foxn1 expression is required for the thymic expansion observed in Rb family mutant mice. Thus, the RB family promotes thymic involution and controls T cell production via a bone marrow-independent mechanism, identifying a novel pathway to target to increase thymic function in patients.

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